

Multivalent Neoglycoconjugates by Regiospecific Cycloaddition of Alkynes and Azides Using Organic-Soluble Copper Catalysts

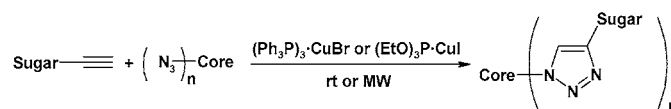
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ABSTRACT



The construction of multivalent neoglycoconjugates is efficiently achieved by the regiospecific catalytic cycloaddition of alkynes and azides using the organic-soluble copper complexes $(\text{Ph}_3\text{P})_3\text{CuBr}$ and $(\text{EtO})_3\text{P-CuI}$. The simultaneous use of microwave irradiation shortened notably the reaction times.

In the fields of glycobiology and supramolecular chemistry, the construction of large molecules with a well-defined architecture such as multivalent ligands¹ or artificial receptors² is normally required. Multivalency in ligand–receptor interactions is an important principle used by Nature to increase weak interactions to biologically relevant levels.³ The principle, normally referred to as the cluster effect, is especially prevalent in carbohydrate recognition events, in which monovalent affinities are generally quite low and such an enhancement is required.⁴ This has been used in the design

of biologically active compounds to endow them with binding power greater than that of their monovalent counterparts. In this respect, glycodendrimers are growing in importance as a class of dendrimers and glycoconjugates.⁵

The synthetic effort normally required to prepare effective, rationally designed, polyvalent ligands are normally high where the use of simple and efficient reactions for the covalent connection of the different modules is a necessity. Driven by this need to develop efficient methodologies, we have demonstrated⁶ in the past that 1,3-dipolar cycloadditions are an efficient and highly versatile strategy for the construction of a variety of multivalent structures such as sugars heterodimers, glycoclusters, calix-sugars, multicalixarenes, and glycocyclodextrins. The approaches used were based on the thermal coupling of alkynes and azides or nitrile oxides as the 1,3-dipolar functions allowing the creation of 1,2,3-

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Table 1. Synthesis of Divalent Neoglycoconjugates

entry	R ¹	R ² / core	product	conditions ^a	t (min/h)	yield (%)
$\text{R}^1\text{-C}\equiv\text{C} + \text{N}_3\text{-R}^2 \longrightarrow \text{R}^1\text{-C}_4\text{N}_3\text{-R}^2 \text{ (3)}$						
1			3a	A	34 min	86
2			3b	B	15 min	99
3			3c	C	45 min	51
			3c	B	26 min	96
$\text{R}^1\text{-C}\equiv\text{C} + \text{N}_3\text{-R}^2\text{-N}_3 \longrightarrow \text{R}^1\text{-C}_4\text{N}_3\text{-R}^2\text{-N}_3\text{-C}_4\text{N}_3\text{-R}^1 \text{ (5)}$						
4			5a	A	11 min	93
5			5b	A	8 min	80
6			5c	C	12 min	83
			5c	B	12 min	86

^a Conditions: (A) (Ph₃P)₃·CuBr, DIPEA, MW; (B) (EtO)₃P·CuI, DIPEA, MW; (C) (Ph₃P)₃·CuBr, DBU, MW; (D) (Ph₃P)₃·CuBr, ICu, DIPEA, MW. For experimental details, see General Procedure and Supporting Information.

triazoles or 1,2-oxazoles as aromatic heterocyclic bridges between the different units that are coupled.⁷ However, a limitation of this approach is the absence of regioselectivity normally found in thermal 1,3-cycloaddition of nonsymmetrical alkynes that leads to the isolation of a mixture of the different possible regioisomers. Also, long reaction times are required in the majority of the cases. In this communication, we contribute new advances regarding the enhancement of the selectivity and shorten the reaction times.

The improvement of the intrinsically poor regioselectivity of the dipolar cycloaddition involving nonsymmetrical alkynes has been addressed in the past with varying success.⁸

A major advance has recently been achieved parallel to our investigations through the use of copper(I)-catalyzed reactions,⁹ which lead only to the 1,4-disubstituted 1,2,3-triazole. To broaden this methodology, we focused our attention in the use of organic-soluble copper(I) complexes that can act as a catalyst allowing homogeneous reactions. Among the copper compounds already reported, we chose (Ph₃P)₃·CuBr^{10a} and (EtO)₃P·CuI^{10b} due especially to their air stability and easy and inexpensive preparation. In addition, it was thought that in order to improve the assemblies and especially to shorten the reactions times, the reactions could also be simultaneously assisted by the use of microwave irradiation.

(7) Presence of an aromatic heterocyclic group next to the glycosidic bond has been pointed out as contributing positively to the interaction of neoglycoconjugates with lectins by increasing the hydrophobicity. See ref 5d.

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Table 2. Synthesis of Multivalent Neoglycoconjugates

entry	R ¹	R ² / core	product	conditions ^a	t (min/h)	yield (%)
		$(N_3)_n$ -Core (6)	Core $\left(\begin{array}{c} R^1 \\ \diagdown \\ N \\ \diagup \\ N \\ \diagdown \\ N \end{array} \right)_n$ (7)			
1			7a	A E	6 min 24 h	53 48
2			7b	A E	6 min 72 h	85 88
3			7c	A B	30 min 20 min	58 77
4			7d	D B	74 min 3 h	77 80
5			7e	D B	30 min 30 min	89 94
6			7f	B	30 min	73

^a Conditions: (A) (Ph₃P)₃·CuBr, DIPEA, MW; (B) (EtO)₃P·CuI, DIPEA, MW; (C) (Ph₃P)₃·CuBr, DBU, MW; (D) (Ph₃P)₃·CuBr, ICu, DIPEA, MW; (E) (Ph₃P)₃·CuBr, DIPEA, rt. For experimental details, see General Procedure and Supporting Information.

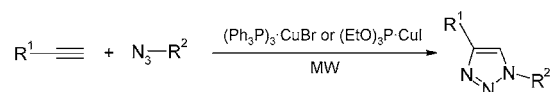
Microwave-assisted organic reactions are rapidly becoming recognized as a valuable tool for facilitating a wide variety of transformations.¹¹ We found that the combination of microwave irradiation with the use of both copper complexes, when used in catalytic amounts, allowed in short reaction times the coupling of a wide variety of alkynes and azides leading in all cases regioselectively to the 1,4-disubstituted 1,2,3-triazoles.¹²

The utility of this methodology is first revealed by the examples in Table 1. The study was initiated by the synthesis

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of divalent mannopyranosylated ligands following two different approaches. First, the direct assembly of functionalized

Scheme 1. Regiospecific Coupling of Alkynes and Azides



sugars was achieved by reaction of alkynyl and azide glycosides. To this end propargyl, thiopropargyl, and aminopropargyl glycosides **1a–c** were chosen to investigate not only the influence of the glycosidic linkage in the coupling by changing the electronic nature of the alkyne but also as

(12) NOE difference spectroscopy has been used for the unambiguous assignment as the 1,4-regioisomer in selected cases.

a way to obtain divalent ligands containing S- and N-glycosides.¹³ In these cases, the assembly proceeds to completion in reaction times no longer than 45 min leading to the 1,4-disubstituted 1,2,3-triazoles **3a–c** with good to almost quantitative yields. It was observed that alkyne **1a**, which supports the more electronegative substituent, reacts well with $(\text{Ph}_3\text{P})_3\cdot\text{CuBr}-\text{DIPEA}$, but no reaction was detected when **1b** and **1c** were used. However, that problem was overcome in the case of **1c** by using a stronger base such as DBU when using $(\text{Ph}_3\text{P})_3\cdot\text{CuBr}$ (entry 3). This result was not found in the reactions with $(\text{EtO})_3\text{P}\cdot\text{CuI}-\text{DIPEA}$, the 1,2,3-triazoles **3b** and **3c** being isolated in almost quantitative yields (entries 2 and 3).

As a second approach for the synthesis of divalent mannosylated ligands, the noncarbohydrate diazides **4a,b** were used in the cycloaddition reaction with the propargyl and thiopropargyl mannosides **1a,b** (entries 4–6) obtaining **5a–c** with similarly good results as in the previous cases.

The synthesis of tri-, tetra-, and hexavalent mannopyranosylated ligands was also easily feasible by using the polyazides **6a–c** (see Table 2). Propargyl mannoside **1a** was scaffolded on those aromatic cores, and the corresponding multivalent ligands **7a–c** (entries 1–3) were obtained in moderate to good yields when the reactions were microwave-assisted, despite the steric congestion inherent to these systems. The synthesis of monovalent and heptavalent glycocyclodextrins was also easily achieved (entries 4–6). Although earlier experiments revealed that the reactions of peracetylated mono-(C-6)-azido **6d** and per-(C-6)-azido β -cyclodextrin **6e** with propargyl and thiopropargyl mannosides **1a,b** were quite slow in the presence of $(\text{Ph}_3\text{P})_3\cdot\text{CuBr}-\text{DIPEA}$, this difficulty could be circumvented by the addition of a catalytic amount of CuI (10% mol) or by the use of $(\text{EtO})_3\text{P}\cdot\text{CuI}-\text{DIPEA}$. Under these conditions, the branched β -cyclodextrins **7d–f** were formed in high yields.

With the aim of further demonstrating the efficiency of the copper catalysts in some selected cases (entries 1 and 2, Table 2), the reactions were performed without the assistance of the microwave irradiation at room temperature. The

(13) Substitution of the natural *O*-glycosides by *S*- or *C*-glycosides is a normal alternative in the synthesis of carbohydrate mimics in order to enhance the stability of the glycosidic linkage towards enzymatic hydrolysis: Bertozzi, C. R.; Bednarski, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 5543.

catalyst proved to be equally efficient and regioselective even if longer reaction times were required as expected, with **7a,b** being isolated in yields similar to those observed in the microwave-irradiated reactions.

The experimental procedure¹⁴ for the microwave-assisted reactions is simple, requiring only the mixture of the reagents, the microwave irradiation, and the evaporation of the solvent prior to the direct purification by a short flash column chromatography. Formation of undesired byproducts was never observed.

In conclusion, it has been established that the construction of well-defined multivalent neoglycoconjugates can easily and effectively be performed by using the cycloaddition reactions of alkynes and azides for the assembly of the different components when using the copper complexes $(\text{Ph}_3\text{P})_3\cdot\text{CuBr}$ and $(\text{EtO})_3\text{P}\cdot\text{CuI}$ as organic soluble catalysts that allow the regioselective formation of 1,4-disubstituted 1,2,3-triazole connections. Although the catalytic features of these copper complexes are fully expressed when the “connection” of alkynes and azides are carried out at room temperature, their combination with microwave irradiation shortens the reaction times considerably. Other remarkable features of the procedure are its simplicity together with the easy and inexpensive preparation and air stability of the catalysts.

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Supporting Information Available: Detailed experimental procedure and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) **General Procedure.** A solution of the alkyne (1.1 mmol) and the azide derivative (1 mmol), DIPEA or DBU (3 mmol), and the copper catalyst [$(\text{Ph}_3\text{P})_3\cdot\text{CuBr}$ or $(\text{EtO})_3\text{P}\cdot\text{CuI}$] (10–20 mmol %) in toluene (25 mL) was irradiated at 850 W (100% power) in a microwave oven (LG MG-5507D) for periods of 2 min, allowing the solution to cool heating intervals, until TLC or the IR spectra of the reaction mixture showed complete disappearance of the starting material. The reaction mixture was evaporated and the crude purified in a short flash column chromatography to yield the 1,2,3-triazole derivative.